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EFFECTS OF PHYSALIS ALKEKENGI, AERIAL PARTS EXTRACTS, ON MORPHINE WITHDRAWAL SYNDROME IN MICE.

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Summary

The effect of *Physalis alkekengi* aerial part extract on the withdrawal syndrome was determined in mice. After induction of dependency by morphine, mice were intraperitoneally administered different concentrations of *Physalis alkekengi* extract (dichloromethane, methanol and waterf). Morphine-withdrawal, induced by naloxone, was assessed by recording the incidence of escape jumps for 60 minutes. All the concentrations of the methanol extract produced statistically significant decrease in development of morphine dependence compared to the control group. Aqueous extract also induced jumping decrease in mice of test group at doses 50, 100 and 200 mg/ kg. We can therefore suggest this plant using successfully in treatment of addiction.

Keywords: Morphine, withdrawal, *Physalis alkekengi*, Jumping

Introduction

Physical dependence is a normal and predictable neurophysiological response to regular treatment with opioids for more than 1-2 weeks duration, continuous or near continuous opioid blood levels. Physical dependence is characterized by a withdrawal syndrome when the opioid is abruptly discontinued, if an opioid antagonist (naloxone) is given, or when drug blood levels fall below a critical level. Withdrawal can also be caused by administration of a mixed agonist-antagonist (*e.g.* buprenorphine, butorphanol, nalbuphine, pentazocine) (1). Opioid dependence is a serious problem in the world and widespread in Asia and Europe (2). Dopaminergic, adrenergic, excitatory amino acids, purinergic, nitric oxide and serotoninergic systems are the systems involved in the withdrawal syndrome of morphine (3). *Physalis alkekengi* L. winter cherry belongs to the Solanaceae family, has been used as a remedy for headache, earache, fever, ulcers, spleen disorders, wound pustules, intestinal pains, purgative and diuretic. This plants contained physalin (13,14-seco-16,24-cycloergostane) that inhibit tumour growth and show antimicrobial activity against *Mycobacterium* (4-6).

Although, the ripe fruits of *Physalis alkekengi* are reported as winter cherry fruits, Ashwagandha or Indian ginseng (*Withania somnifera* which reported as an effective plant on morphine withdrawal syndrome), known as winter cherry too (7-9). Also some medicinal plants including ginseng (10), passion flower (11), *Salvia leriifolia* (12) and *Ferula gummosa* (13) have been studied in this regard. The plant, *Physalis alkekengi*, is traditionally used to alleviate opium withdrawal syndrome. This study was aimed to find pharmacological support for this usage.

Material and Methods

Plant material

Aerial parts of *Physalis alkekengi* were collected in July 2008 from Mazandaran province near to Noshahr in north of Iran. A voucher specimen was preserved for further reference at the Herbarium of Medicinal Plants Research Center, Tehran University of Medical Sciences, Iran.

Preparation of the extracts

Air-dried aerial parts of the plant (800g) were cut in to small pieces and percolated consequently with dichloromethane, methanol and water. After filtering, the solutions were concentrated under reduced pressure to gain dichloromethane (4 g), methanol (12 g) and water (3 g), respectively.

Animals

Male albino mice weighing 20-30 g were purchased from Pasteur institute (Tehran, Iran) and maintained in animal house under standard condition in 12h / 12h light dark cycle at 25 ± 3 °C. They received standard pellet diet and water *ad libitum*. Animal handling was performed as per *Good Laboratory Practice*. Research proposal was prepared based on the CPCSEA (Committee for the Perpose of Control and Supervision of Experiments on Animal) and approved by IAEC (Institutional Animal Ethical Committee) of Tehran University of Medical Sciences.

Administration of the extracts

The mice were randomly divided in to 16 groups of six in each. All animals were rendered dependent on morphine. All the animals were injected subcutaneously (sc) with morphine at doses of 50, 50 and 7m (mg/ kg) three times daily for three days. On the forth day, one dose of morphine (50 mg/ kg) was injected to all groups before treatment with naloxone. After induction of morphine dependence, normal saline was injected to control group (3 ml, ip). Various concentration (12.5, 25, 50, 100 and 200 mg/ kg) of the extracts were injected to another groups. Two hours after the final administration of morphine, the withdrawal sign were appeared by injection of naloxone (5 mg/ kg, sc). Immediately, the number of jumping episode was counted for 60 minutes (3, 14, 15).

Statistical analysis

The data were expressed as Mean ± SEM. One-way ANOVA was used for comparison of the data followed by the multiple comparison Tukey-Kramer test and P values less than 0.05 were considered significant. All statistical calculations were done with SPSS for windows (SPSS, version10) software.

Results and Discussion

The effect of *Physalis alkekengi* extracts (dichloromethane, methanol and aqueous) on the morphine-withdrawal jumps in mice is shown in Figures 1, 2 and 3. Jumping is a sign of the development of dependence to opioid drugs.

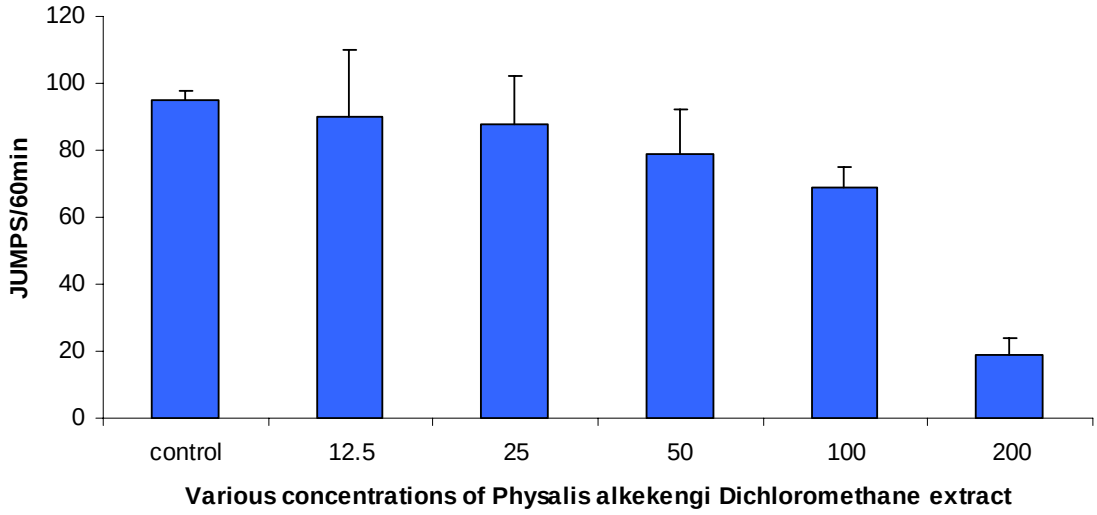

Fig.1. Correlation between morphine withdrawal jumps per 60 min (Mean ± SEM) and different concentration of the plant dichloromethane extract. Significant differences between test (at dose of 200 mg/ kg) and control groups are shown as P value<0.05.

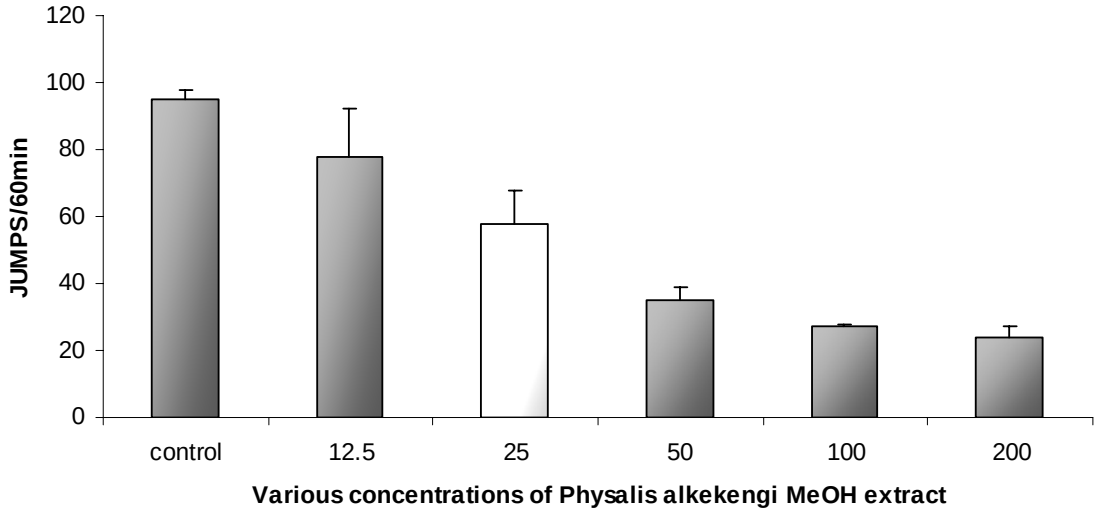

Fig.2. Relation between morphine withdrawal jumps per 60 min (Mean ± SEM) and different concentration of the plant methanol extract. Significant differences between test (at all doses) and control groups are shown as P value<0.05.

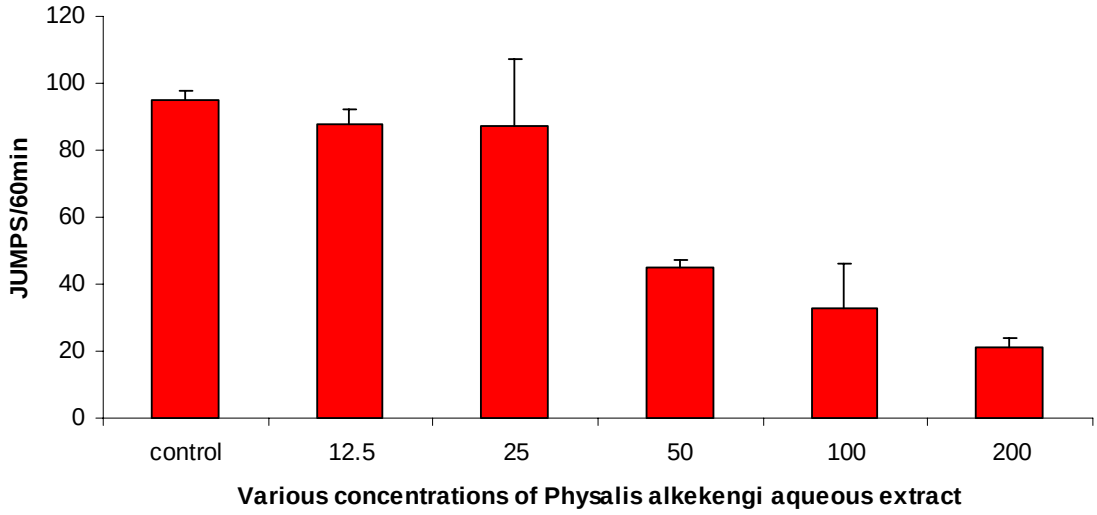

Fig.3. Correlation between morphine withdrawal jumps per 60 min (Mean ± SEM) and different concentration of the plant aqueous extract. Significant differences between test (at doses 50, 100 and 200 mg/ kg) and control groups are shown as P value<0.05.

A significant difference between dichloromethane group (at dose of 200 mg/ kg) and control was shown but lower doses were not effective (**Fig.1**). All the concentrations of the methanol extract produced statistically significant decrease in development of morphine dependence compared to the control groups. Protective effect was generally dose-dependent (**Fig.2**). A significant decrease ($p < 0.05$) was observed in the morphine withdrawal jumps by decreasing the concentration of the extract. Aqueous extract also induced jumping decrease in mice of test group at doses 50, 100 and 200 mg/ kg (**Fig.3**). The highest activity showed in all extracts of *Physalis alkekengi* at 200 mg/kg i.p. which inhibited more than 94% incidence of escape jumps (for 60 minutes).

There are several lines of evidence implying the involvement of the central glutamatergic system in morphine dependence (16). Benzodiazepines, via $GABA_A$ receptors, had an inhibitory effect on the dependence on morphine (17). *Physalis angulata* produce marked antinociception against the acetic acid-induced visceral pain and inflammatory pain responses induced by formalin in mice (18). Detailed mechanism of compounds, involved in antinociception and morphine dependency inhibition, is not clear now.

Withanolides comprise eight structural kinds of naturally occurring C28 steroidal lactones exhibiting different biological activities. These compounds are produced mainly, but not exclusively by some genera of the Solanaceae family. Amongst these genera, *Physalis* is highlighted since they contain greatest variety of withasteroids known so far (19). Previously, inhibition of morphine tolerance and dependence was reported from *Withania somnifera* (Solanaceae) in mice (9). It seems that withanolides might be one of the causative and effective compounds in morphine dependency inhibition in both *Withania* and *Physalis* genus.

In conclusion, the aqueous and ethanol extracts of *Physalis alkekengi* aerial parts could suppress morphine withdrawal syndrome. The results of this study are valuable as one step towards the research for different mechanisms of action that may be involved in the inhibitory effect of the extracts on morphine dependency.

Acknowledgments

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